UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,827	10/23/2001	John Jacob Schwartz	FLG-002	6161

51414 7590 09/12/2006

GOODWIN PROCTER LLP
PATENT ADMINISTRATOR
EXCHANGE PLACE
BOSTON, MA 02109-2881

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,827	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *13,14,17,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15,16,18-28 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/20/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 6/15/2006, in which claims 34-97 were canceled. Currently, claims 1-33 are pending.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-33) and the species "DNA sequence operably linked to a target gene" as the species of target biomolecule and "zinc finger" as the species of interaction domain in the reply filed on 6/15/2006 is acknowledged. The reply indicates that claims 1-12, 15, 16, 18-28 and 31-33 are readable upon the elected species.

Claims 13, 14, 17, 29 and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/15/2006.

An examination on the merits of claims 1-12, 15, 16, 18-28 and 31-33 follows.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 5/20/2002, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It was not executed in accordance with either 37 CFR 1.66 or 1.68. John Schwartz and Ruchira Das Gupta have not signed the declaration.

Specification

The disclosure is objected to because of the following informalities: the name "Rebar" is misspelled at page 23, paragraph [0065].

Appropriate correction is required.

Claim Objections

Claims 2, 3, 5-12, 15, 16, 19, 20, 22-28 and 31-33 are objected to because of the following informalities: the claims should refer back to "the chimeric protein" of a previous claim rather than "a chimeric protein" so that it is clear that the dependent claims refer back to the chimeric protein of a prior claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 15, 16, 18-28 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a set of chimeric proteins comprising an interaction domain that binds to a target biomolecule and a ligand binding domain comprising a peptide that binds to a preselected ligand. The ligand binding domain is claimed as a peptide identified by using a recombinant display technique to screen for peptides capable of binding the preselected ligand. Further, binding of the ligand to the ligand binding domain must be capable of inducing a change in the chimeric protein such that binding of the interaction domain to the target biomolecule is regulated by the ligand. Dependent claim 2 further limits the recombinant display technique to one selected from the group consisting of phage display, single chain antibody display, retroviral display, bacterial surface display, yeast surface display, ribosome display, two-hybrid techniques, three-hybrid techniques and derivatives thereof. Dependent claim 3, further limits the ligand binding domain to a peptide of no more than one hundred amino acids in length.

Claim 4 is drawn to a set of chimeric proteins comprising an interaction domain that binds a target biomolecule and a detection domain comprising a peptide that recognizes a stimulus. The claim further requires that the detection domain be no greater than one hundred amino acids in length. Upon receipt of the stimulus, the detection domain must alter the binding of the interaction domain to the target biomolecule. Claim 5 further defines the detection domain peptide as one that is selected using a recombinant display technique. Claims 6 and 7 require the detection domain to be responsive to perturbation of a thermodynamic state or electromagnetic radiation, respectively. Claims 8-11 limit the size of the detection domain to not more than 80, 60, 40 or 20 amino acids, respectively.

Claims 1-11 read on any target biomolecule of any structure. Claim 12 limits the target biomolecule of claim 1, 3, or 4 to a DNA sequence operably linked to a target gene, where the chimeric protein regulates expression of the target gene.

Claim 15 requires the chimeric protein of claim 1, 3, or 4 to further comprise a dimerization domain, and claim 16 limits the chimeric proteins to those that require dimerization for efficient binding to the target biomolecule and where the ligand binding to the ligand binding domain regulates a change that regulates dimerization.

Claim 18 is drawn to a set of chimeric proteins comprising an interaction domain that binds to a DNA sequence operably linked to a target gene to regulate expression of the target gene, and a ligand binding domain comprising a peptide that binds to a ligand. The ligand binding domain is claimed as a peptide identified by using a recombinant display technique to screen for peptides capable of binding the ligand. The protein must be constructed such that binding of the ligand to the ligand binding domain results in a change in the chimeric protein resulting in a regulation of binding of the interaction domain to the DNA sequence thereby modulating transcription of the target gene. Claim 19 further limits the recombinant display technique to one selected from the group consisting of phage display, single chain antibody display, retroviral display, bacterial surface display, yeast surface display, ribosome display, two-hybrid techniques, three-hybrid techniques and derivatives thereof. Claim 20 limits the size of the ligand binding domain to a peptide of no more than one hundred amino acids.

Claim 21 is drawn to a set of chimeric proteins comprising an interaction domain that binds to a DNA sequence operably linked to a target gene to regulate expression of the target gene, and a detection domain comprising a peptide that is responsive to a stimulus. The peptide

responsive to the stimulus can be no more than 100 amino acids in length, and the stimulus must produce a change in binding of the interaction domain to the DNA sequence to modulate the transcription of the target gene. Claim 22 limits the detection domain to a peptide identified by a recombinant display technique. Claims 23 and 24 require the detection domain to be responsive to perturbation of a thermodynamic state or electromagnetic radiation, respectively. Claims 25-28 limit the size of the detection domain to not more than 80, 60, 40 or 20 amino acids, respectively.

Claim 31 limits the interaction domain of the chimeric proteins of claim 18, 20 or 21 to a zinc finger motif. Claim 32 requires the chimeric proteins of claim 18, 20 or 21 to comprise a dimerization domain, and claim 33 requires the binding of a ligand or detection of a stimulus to result in a change in the protein that regulates the dimerization of the protein thereby regulating DNA binding.

Accordingly, the claims encompass an enormous genus of chimeric proteins that comprise two domains defined by function: (1) an interaction domain, and (2) a detection domain, which encompasses ligand binding domains and stimulus-responsive domains. The binding of the interaction domain to its target biomolecule must be conditional upon the detection of a stimulus or ligand by the detection/ligand binding domain. The proteins must be capable of recognizing a genus of ligands and genus of stimuli, including electromagnetic radiation and thermodynamic perturbations. The proteins must be capable of interacting with a genus of target biomolecules, including a genus of DNA sequences. Thus, the claims encompass an enormous genus of chimeric proteins defined by function.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes TBD-cI-bZIP protein, which comprises a taxol binding domain of 12 amino acids of Bcl2 protein, amino acids 133-236 of the lambda repressor, and a 32 amino acid leucine zipper motif from the *S. cerevisiae* transcription factor GCN4 (e.g. paragraphs [0167] and [0168]). The TBD-cI-bZIP protein was tested for its ability to respond to taxol ligand, and it was demonstrated that taxol binding modulates the DNA binding activity of the transcriptional repressor (e.g. paragraph [0184]). No description is provided of any other chimeric protein that meets the structural and functional limitations of the claims.

The specification envisions using detection domains that are responsive to ligand binding, such as a biomolecule, synthetic chemical, an ion, or an electron, or a stimulus, such as a change in thermodynamic state or electromagnetic radiation (e.g. paragraph [0052]). With regard to thermodynamic states, the specification envisions changes in pressure and temperature (e.g. paragraph [0052]). With regard to electromagnetic radiation, the specification envisions a pulse of light, a decrease in light intensity, or a change in wavelength (e.g. paragraph [0052]). The specification does not specifically describe detection domains that are capable of detecting these stimuli and affecting the binding of the interaction domain to a target biomolecule. The specification suggests that the domains may be derived from known proteins or may be obtained in a screen for peptides that have the desired function (e.g. paragraphs [0053]-[0061]). With respect to the interaction domain, the specification envisions using interaction domains capable

of binding DNA, RNA, protein, carbohydrates and lipids (e.g. paragraph [0063]). The specification provides numerous examples of DNA binding domains obtained from transcription factors known in the art (e.g. paragraphs [0063]-[0065] and [0072]-[0083]). To place the detection domain and interaction domain at a position that causes the binding of the interaction domain to a target biomolecule to be conditional on the presence or absence of a stimulus, the specification envisions using structural data (e.g. threading) and functional data (e.g. paragraphs [0066-0071]). Ultimately, the chimeric protein needs to be tested in a functional assay to determine whether modulation of the interaction domain is conditional upon detection of a stimulus or ligand (e.g. page 27, lines 12-20; paragraph [0104]). With respect to chimeric proteins responsive to temperature, the specification envisions "chimeric protein 40," a protein that undergoes a conformational change in response to an increase in temperature, resulting in the loss of binding to an input site (e.g. paragraph [0147]; Figure 9). With respect to chimeric proteins responsive to radiation, the specification envisions "chimeric protein 50," a protein that will be prevented from binding to binding site I_2 in the presence of UV or other type of irradiation (e.g. paragraph [0147]; Figure 9). The specification does not describe the amino acid sequences of chimeric proteins 40 and 50 and does not identify the different domains used to make these proteins.

Even if one accepts that the example described in the specification meets the claim limitations of the rejected claims with regard to structure and function, the example is only representative of a single chimeric protein that meets the limitations of the claims. The results are not necessarily predictive of other chimeric proteins composed of different interaction domains and/or detection domains. Thus, it is impossible for one to extrapolate from the

example described herein a representative number of chimeric proteins that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of detection domains that confer a conformational change to a protein such that the interaction of an interaction domain and a biomolecule is modulated. For example, it was known in the art at the time the invention was made that heat shock factor 1 (HSF1) is a stress-responsive factor that oligomerizes and acquires DNA binding activity in response to stress (Shi et al. Molecular and Cellular Biology, Vol. 15, No. 8, 4309-4318; e.g. page 4309, right column, 1st paragraph). However, the ability of the HSF1 protein to bind DNA only upon a stress stimulus is lost upon fusion of the protein or portion of the protein to a GAL4 DNA binding domain; the GAL4-HSF1 chimeric proteins are constitutively bound to DNA (e.g. page 4315, Heat shock does not influence the DNA-binding activity of the GAL4-HSF1 protein). Furthermore, the ligand binding domains of steroid hormone receptors and proteins such as AraC, which are capable of altering DNA binding activity of a coupled DNA binding domain upon the binding of a ligand, are larger than 100 amino acids (GenBank entry for NP_724460, ligand binding domain amino acids 465-624; Soisson et al. J. Mol. Biol., Vol. 273, pages 226-237, 1997). With respect to detection domains capable of modulating DNA binding activity conditional upon a light stimulus, Mendelsohn (Nature Biotechnology, Vol. 20, pages 985-987, 2002) teaches that light-based transcription control was a long-anticipated system that was not reduced to practice until the work of Shimizu-Sato et al, which was published in Nature Biotechnology in 2002 subsequent to the effective filing date of the instant application. This invention is also disclosed in US Patent No. 6,858,429. Furthermore, Fetrow teaches (Fetrow et

al., J. Mol. Biol., Vol. 282, pages 703-711, 1998) that although function prediction by homology to previously characterized proteins is extremely successful and is fast, cheap and reliable, there are several problems that limit its potential utility, one of which is that sequence homology does not guarantee functional similarity (p. 704, left column, first full paragraph). Fetrow teaches that "threading" (analyses using structure prediction tools) can identify topological cousins, that is, protein families such with similar structures, but dissimilar functions. Fetrow teaches using a three dimensional descriptor of the active site of a protein, termed "fuzzy functional form" (FFF) and argues that threading alone is not enough to provide the required information about function because it has been show that pairs of proteins can have similar structures but unrelated functions (page 706, right column, last paragraph). Fetrow teaches that because topological cousins exist, knowledge of the structure is not equivalent to identification of protein function. While the instant specification envisions using sequence alignments and threading to combine known elements and predict the resulting function, more than conceptual manipulation of known sequences is required to put one in possession of a representative number of species of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of chimeric proteins, and therefore conception is

not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Given the very large genus of chimeric proteins encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to structure necessary to confer the claimed functions, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of chimeric proteins. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those chimeric proteins that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 1-12, 15, 16, 18-28 and 31-33.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 12, 15, 16, 18, 19 and 31-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Evans et al (US Patent No. 6,333,318; see the entire reference).

Regarding claims 1, 2, 18 and 19, Evans et al teach a chimeric protein comprising a DNA-binding domain that binds to a target DNA sequence, a ligand binding domain that binds to a preselected ecdysteroid, and a transactivation domain, wherein binding of the ligand binding domain to ecdysteroid results in a change that regulates the binding of the DNA binding domain to the target DNA sequence (e.g. column 7, lines 52-62; column 8, lines 7-34; paragraph bridging columns 8-9; column 10, lines 29-62; column 11, line 53 to column 12, line 42; Example 1). The ligand binding domains taught by Evans et al meet the limitation of the claim with regard to the phrase "ligand binding domain comprising a peptide that binds to a preselected ligand, selection of said peptide for binding being informed by a recombinant display technique," because the selection process would not alter the structure of the ligand binding domains taught by Evans et al. If one were to include those peptides in a screen for binding to an ecdysteroid, the peptide would bind without any structural modification. Thus, the teachings of Evans et al meet each of the limitations of claims 1, 2, 18 and 19.

Regarding claim 12, the DNA target sequence is operably linked to a target gene and the chimeric protein regulates expression of the target gene (e.g. column 20, line 53 to column 22, line 9; Example 1).

Regarding claims 15, 16, 32 and 33, the chimeric proteins taught by Evans et al comprise a dimerization domain capable of heterodimerization or homodimerization, and the binding of an ecdysteroid to the ligand binding domain of the chimeric protein regulates the ability of the chimeric protein to dimerize (e.g. column 11, line 47 to column 12, line 43).

Regarding claim 31, Evans et al teach DNA binding domains (i.e. interaction domains) comprising zinc finger motifs (e.g. column 8, line 60 to column 10, line 60; Example 1).

Claims 1, 2, 12, 15, 18, 19, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Bustos et al (PNAS, USA, Vol. 90, pages 5638-5642, 1993; see the entire reference).

Regarding claims 1, 2, 18 and 19, Bustos et al teach a chimeric protein, $AraC_{Dimer}$-$LexA_{DNA}$, comprising a LexA DNA binding domain (interaction domain) and an AraC ligand binding/dimerization domain (e.g. page 5641, right column; Figure 2). Further, Bustos et al teach that arabinose binds to the chimeric protein and increases the binding of the protein to a LexA operator sequence (e.g. page 5641, right column; Figure 5). The AraC ligand binding domain taught by Bustos et al meets the limitation of the claim with regard to the phrase "ligand binding domain comprising a peptide that binds to a preselected ligand, selection of said peptide for binding being informed by a recombinant display technique," because the selection process would not alter the structure of the ligand binding domain taught by Bustos et al. If one were to include the AraC peptides in a screen for binding to arabinose, the peptide would bind without any structural modification. Thus, the teachings of Bustos et al meet each of the limitations of claims 1, 2, 18 and 19.

Regarding claim 12, Bustos et al teach that the target biomolecule is a LexA operator sequence operably linked to a LacZ target gene (e.g. page 5639, left column, 1st full paragraph and paragraph bridging columns; Figure 5).

Regarding claims 15, 32 and 33, Bustos et al teach that the chimeric protein contains a dimerization domain which is required for DNA binding (e.g. page 5641, right column; Figure 2).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER